

Bridging the Evidence Gap: A Systematic Review and Model-based Meta-analysis of Medication Safety and Pharmacokinetics in Pregnancy

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Abstract

The safe and effective use of medications during pregnancy remains a critical challenge in perinatal medicine, where physiological changes alter maternal pharmacokinetics (PKs) and fetal exposure in ways that are poorly captured by current clinical guidance. We conducted a systematic review to evaluate the safety, PKs, and model-informed dosing of medications during pregnancy, bridging mechanistic, clinical, and epidemiologic evidence. Comprehensive searches of MEDLINE, Embase, CENTRAL, Web of Science, ClinicalTrials.gov, European Union EU Clinical Trials Register, World Health Organization International Clinical Trials Registry Platform, Food and Drug Administration/European Medicines Agency labeling, and teratology information services were performed for the years 2000–2025, with final searches in September 2025. Eligible studies included systematic reviews, population or physiologically based PK (PBPK) models, prospective and retrospective cohorts, and clinical PK studies reporting maternal or fetal drug exposure and safety outcomes. Screening, extraction, and risk of bias assessments (AMSTAR-2, ROBIS, Newcastle–Ottawa Scale, and PBPK reporting checklist) were conducted in duplicate with conflict adjudication. Forty-one studies met the inclusion criteria, comprising nine systematic reviews, eight large epidemiologic cohorts, seven clinical PK investigations, and seventeen model-based studies. Core evidence synthesized across 20 high-quality studies revealed consistent reductions in drug exposure for antiepileptics, antivirals, antihypertensives, and psychotropics during pregnancy, with implications for therapeutic drug monitoring, dose adjustment, and maternal–fetal safety. Modeling frameworks increasingly informed dosing recommendations, but external validation remained limited. Evidence gaps were identified in antihypertensives, immunotherapies, and pregnancy-specific drug–drug interactions. This review highlights the urgent need for integrated model-informed strategies, standardized maternal–fetal pharmacology endpoints, and coordinated international data resources to ensure safe and effective medication use in pregnancy.

Keywords: Maternal–fetal medicine, medication safety, modeling, physiologically based pharmacokinetic, pregnancy pharmacokinetics, systematic review

INTRODUCTION

The safe and effective use of medications during pregnancy is a central challenge in perinatal medicine. Profound physiological changes across gestation alter absorption, distribution, metabolism, and excretion of drugs, leading to unpredictable maternal pharmacokinetics (PKs) and variable

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fetal exposure.^[1] Recent physiologically based PK (PBPK) approaches have begun to predict these changes for key agents such as tenofovir^[1] and ceftazidime,^[2] demonstrating that pregnancy modifies both clearance and volume of distribution in clinically significant ways. Beyond single-drug studies, novel frameworks have sought to integrate developmental origins hypotheses with modern imaging and artificial intelligence (AI) to link prenatal exposures to lifelong health outcomes.^[3] The implications of drug–drug interactions in this unique population are equally critical, with PBPK models quantifying interactions between atazanavir/r and rifampicin.^[4]

Early translational work has advanced maternal–fetal PBPK modeling for diverse therapeutic areas, ranging from antiretrovirals^[1,4] to antiepileptics.^[5] These approaches enable estimation of fetal drug exposure when direct sampling is not feasible^[5] and have already been applied to compare oral versus long-acting injectable antipsychotics.^[6] Minireviews further emphasize both opportunities and limitations of PBPK during pregnancy, highlighting the need for model transparency, stage-specific validation, and clinical integration.^[7] However, most PK studies remain small and fragmented, often conducted postpartum or in narrowly defined populations.^[8] Even widely used drugs such as labetalol continue to lack robust, longitudinal PK characterization in pregnant women.^[9]

Systematic efforts to consolidate this evidence are emerging. Borda *et al.* synthesized over 50 studies to document clinical interventions driven by PK changes across antiretrovirals, antiepileptics, and antihypertensives.^[10] Chaphekar *et al.* provided a structured review of maternal–fetal pharmacology and PBPK applications,^[11] while Chen *et al.* extended PBPK to topiramate, proposing dose adjustments during pregnancy.^[12] Such model-informed strategies are increasingly advocated by pharmacometrics groups,^[13,14] underscoring the value of integrating computational prediction with clinical trial design. Prospective PK studies, such as Faure-Bardon *et al.* on valaciclovir in cytomegalovirus-infected women,^[15] remain rare but provide irreplaceable maternal–cord paired data. Similarly, regulatory PBPK applications have supported dosing guidance for psychotropics like sertraline,^[16] and innovative digital twin systems promise to extend maternal–fetal PK simulation capacity.^[17]

The rapid expansion of this field is evident in applications to novel therapies such as cystic fibrosis modulators^[18] and systematic methodological reviews of exposure quantification.^[19] At the same time, pharmacoepidemiologic studies using parallel retrospective cohorts have prioritized signals for adverse pregnancy outcomes in the context of rising medication use.^[20] Pharmacometrics and systems pharmacology are increasingly positioned to bridge gaps between regulatory decision-making and clinical practice,^[21] as illustrated by antibody dosing optimization,^[22] and large-scale registries such as the American PREGNANCy Mother–Child Cohort^[23] and the Chinese maternal drug exposure birth

cohort.^[24] PBPK extensions now include predictions for zonisamide,^[25] cefuroxime,^[26] famotidine,^[27] and sertraline in perinatal women.^[28]

Safety concerns remain paramount. Updated systematic reviews on antibiotic use in pregnancy^[29] and lamotrigine precision dosing via PBPK^[30] illustrate the dual need to balance teratogenic risks with maternal disease control. Regulatory submissions have increasingly relied on PBPK evidence, as with fostemsavir.^[31] Studies of antidepressants such as amitriptyline^[32] and opioid-use disorder medications such as naltrexone^[33] show that pregnancy modifies both drug metabolism and clinical response. Recent maternal–fetal PBPK models of antiretroviral combinations^[34] and structured PK study design guidance^[35] further strengthen the methodological base. Reviews of pharmacological models for safety assessment^[36] and nationwide register studies of maternal medication use^[37] emphasize both the urgency and the feasibility of scaling evidence. Hybrid experimental–modeling approaches, such as placenta perfusion combined with PBPK for corticosteroids,^[38] exemplify translational innovation. Applications have even extended to immunosuppressants such as tacrolimus,^[39] systematic reviews of antiphospholipid syndrome medications,^[40] and observational cohorts linking drug exposure to pregnancy outcomes.^[41]

Taken together, these 41 studies [Table 1] provide the most comprehensive evidence base to date for understanding how pregnancy alters drug PKs and safety. They span systematic reviews, clinical PK studies, PBPK modeling, and large-scale epidemiology, but also reveal substantial gaps: Few prospective maternal–cord paired studies, limited external validation of models, and underrepresentation of drug classes beyond antiepileptics, antivirals, and psychotropics. The Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA)-aligned search and selection strategy [Table 2] ensured reproducibility and transparency, with dual screening, deduplication, and outreach to consortia for unpublished data. Risk of bias assessment across systematic reviews, cohorts, and modeling studies [Table 3] demonstrated variable quality, but identified a core set of high-quality studies that anchor the synthesis.

The evidence landscape [Figure 1] highlights density in PBPK and population PK (PopPK) modeling since 2024, but stark gaps in antihypertensives, immunotherapies, and pregnancy-specific drug–drug interactions. Mechanistic understanding of pregnancy-driven PK alterations [Figure 2] now permits translation into model-informed dosing recommendations across drug classes [Table 4]. Synthesizing these insights into a model-informed safety and dosing dashboard [Figure 3] demonstrates practice-ready algorithms for lamotrigine, labetalol, and valaciclovir, while flagging modeling-only evidence for immunotherapies and psychotropics.

Medication use during pregnancy is rising globally, yet evidence guiding dosing and safety remains fragmented, outdated, or extrapolated from nonpregnant populations.

Table 1: Core literature supporting the systematic review on medication safety and pharmacokinetics in pregnancy

Author	Study design/type	Drug(s)/class	Population (n/ characteristics)	Exposure and outcome measures	Core findings/contribution	Quality appraisal	Relevance to review aims
Borda <i>et al.</i> ^[10]	Systematic review	Multiple drug classes	50+ studies, global	PK alterations leading to dose adjustments	Synthesized clinical interventions prompted by PK shifts; gaps across ARVs, AEDs, antihypertensives	AMSTAR-2: High; ROBIS: Low risk	Anchors' rationale for dose-optimization review
Nguyen <i>et al.</i> ^[29]	Systematic review	Antibiotics	100+ studies	Drug safety in pregnancy	Updated antibiotic safety evidence; highlights underrepresented drug classes	AMSTAR-2: High; ROBIS: Low	Defines safety evidence base for the most common meds
Zarek <i>et al.</i> ^[40]	Systematic review	APS medications	30+ studies	Drug exposure versus pregnancy outcomes	Systematic evidence of undertreatment due to exposure reduction	AMSTAR-2: Moderate-High	Policy relevance; signals risk of discontinuation
Hudson <i>et al.</i> ^[19]	Structured review	Multiple classes	Narrative methods	Exposure quantification methods	Summarized maternal–fetal PK sampling and measurement approaches	Narrative; methods-focused	Provides methodological backbone
Stika and Hebert ^[35]	Methodological guidance	General	Not applicable	PK study design considerations	Outlined design best practices for PK studies in pregnancy	Methods	Improves internal validity of PK cohorts
Li <i>et al.</i> ^[24]	Prospective cohort	Multiple	<i>n</i> ≈113k, China	Drug exposure registry, outcomes	Large-scale prospective data; links exposure to adverse outcomes	NOS: 9/9	Flagship epidemiological evidence
Leal <i>et al.</i> ^[23]	Registry cohort	Multiple	<i>n</i> ≈4.7M, USA	Medication dispensing and outcomes	Massive dataset; prevalence and outcome data	NOS: 9/9	Signal discovery; pharmacoepidemiologic strength
Hwang <i>et al.</i> ^[20]	Retrospective cohorts	Multiple	Large parallel cohorts	Drug exposure versus adverse pregnancy outcomes	Parallel RWD analysis prioritized signals	NOS: 8/9	Modern pharmacosurveillance methods
Zhang <i>et al.</i> ^[41]	Observational cohort	Multiple	<i>n</i> ≈526, China	Trimester drug exposure versus outcomes	Regional evidence; outcome associations identified	NOS: 7/9	Adds geographic diversity
Faure-Bardon <i>et al.</i> ^[15]	Prospective PK	Valaciclovir	<i>n</i> =22 CMV-infected women	Maternal PK, cord: maternal ratios	Quantified maternal–fetal valaciclovir transfer	NOS: 8/9	Rare direct maternal–fetal PK data
Bhamidipaty-Pelosi <i>et al.</i> ^[9]	Prospective PK/PD cohort	Labetalol	<i>n</i> =38, longitudinal	Stereoisomer-specific PK, BP response	Pregnancy-related PK changes and postpartum normalization	NOS: 9/9	Direct PK/PD evidence for antihypertensives
Van der Heijden <i>et al.</i> ^[38]	Hybrid perfusion + PBPK	Corticosteroids	Placenta perfusion (<i>n</i> =12)	Transfer kinetics, dosing simulation	Optimized dosing of antenatal steroids	PBPK checklist: strong	Mechanistic bridge; translational relevance

Contd...

Table 1: Contd...

Author	Study design/type	Drug(s)/class	Population (n/ characteristics)	Exposure and outcome measures	Core findings/contribution	Quality appraisal	Relevance to review aims
Atoyebe <i>et al.</i> ^[4]	PBPK model	ARVs (Atazanavir/r + Rifampicin)	Virtual cohort	Drug–drug interactions	Quantified DDI impact during pregnancy	PBPK checklist	Pregnancy-specific DDI guidance
Hong <i>et al.</i> ^[18]	PBPK model	CF modulators (ETI)	Virtual cohort, CF women	Predicted maternal/fetal exposure	Predicted late-gestation exposure decline; dosing implications	PBPK checklist	Applies PBPK to novel therapies
Qian <i>et al.</i> ^[30]	PBPK model	Lamotrigine	Virtual cohort	UGT induction, PK simulations	Showed 40% reduced exposure in the 3rd trimester	PBPK checklist	Guides dose adjustment, supports TDM
Scherf-Clavel <i>et al.</i> ^[32]	PBPK + clinical data	Amitriptyline	Pregnant women, clinical + model	Maternal and metabolite levels	AMI↑ NOR↓ during pregnancy; monitoring suggested	PBPK checklist	Antidepressant dosing guidance
Abduljalil <i>et al.</i> ^[1]	PBPK model	Tenofovir	Virtual pregnant cohort	Maternal PK prediction	Predicted PK changes; informs ARV dosing	PBPK checklist	Policy-relevant ARV evidence
Abduljalil <i>et al.</i> ^[2]	PBPK model	Ceftazidime	Virtual pregnant cohort	Predicted PK profiles	Projected maternal PK alterations	PBPK checklist	Anti-infective dose projection
Bediako-Kakari <i>et al.</i> ^[6]	PBPK model	Antipsychotics (oral vs. LAI)	Virtual cohort	Fetal exposure estimates	Compared oral versus LAI exposure profiles	PBPK checklist	Fills psychiatry treatment gap
Salem <i>et al.</i> ^[31]	PBPK model	Fostemsavir	Virtual cohort	Pregnancy dosing projections	Model supported regulatory dosing recommendations	PBPK checklist	Regulatory acceptance pathway

Quality appraisal assigned according to study design. NOS: Newcastle–Ottawa Scale, AMSTAR-2: A MeaSurement Tool to Assess Systematic Reviews, ROBIS: Risk of bias in systematic reviews, PBPK: Physiologically Based Pharmacokinetic modelling, LAI: Long-acting injectable, ARV: Antiretroviral, CF: Cystic fibrosis, PK: Pharmacokinetics, TDM: Therapeutic drug monitoring, AMI: Acute myocardial infarction, DDI: Decision-to-delivery interval, ETI: Elexacaftor/Tezacaftor/Ivacaftor, UGT: Uridine 5'-Diphospho-Glucuronosyl Transferase, PD: Pharmacodynamics, CMV: Cytomegalovirus, RWD: Real-world data, APS: Antiphospholipid syndrome, AEDs: Antiepileptic drugs, ↑: Increase, ↓: Decrease

Existing reviews have addressed subsets of drugs or methods, but no comprehensive synthesis has bridged mechanistic PBPK modeling, clinical PKs, and large-scale epidemiology under a unified framework. This systematic review therefore aims to (1) evaluate the safety and PKs of medications during pregnancy across all therapeutic classes studied to date; (2) integrate model-informed predictions with empirical clinical data; (3) assess risk of bias and certainty of evidence using validated tools; and (4) generate practice-relevant dosing and safety recommendations to inform perinatal pharmacology and policy.

METHODOLOGY

Eligibility criteria

We defined the scope of this systematic review according to population, intervention, comparator, outcomes, and study design (PICOS) elements. Eligible studies enrolled pregnant individuals at any gestational age and reported medication PKs, pharmacodynamics, maternal or fetal exposure, or safety outcomes. Interventions of interest included any therapeutic drug classes for which PK or safety data in pregnancy

were available. Comparators were nonpregnant women, inter-trimester differences, or postpartum baselines. Outcomes included maternal drug concentrations (area under the curve [AUC], clearance, C_{max}, C_{min}), cord: Maternal ratios, fetal exposure proxies, therapeutic drug monitoring (TDM) requirements, and pregnancy or neonatal safety outcomes.

We included systematic reviews, meta-analyses, clinical PK studies, prospective and retrospective cohorts, case–control studies, PBPK and PopPK models, and hybrid translational designs such as placenta perfusion combined with modeling. Narrative reviews, case reports, editorials, and conference abstracts without original PK data were excluded. Studies without relevant PK or safety endpoints were also excluded.

Information sources

We searched the following sources from January 2000 to September 2025: MEDLINE (PubMed), Embase, CENTRAL (Cochrane), Web of Science Core Collection, ClinicalTrials.gov, European Union Clinical Trials Register, World Health Organization International Clinical Trials Registry Platform, and the Cochrane Pregnancy and Childbirth

Table 2: Preferred reporting items for systematic reviews and meta-analyses – aligned search strategy and information sources

Source/ register	Full query string (verbatim)	Limits/filters applied	Automation/ de-duplication	Gray literature and org outreach	Backward/ forward citation tracking	Contacted investigators/ consortia	Data/code availability
MEDLINE (PubMed)	((“Pregnancy”[Mesh] OR pregnan* OR gestation* OR antenatal OR perinatal) AND (“Pharmacokinetics”[Mesh] OR pharmacokinetic* OR “population pharmacokinetic*” OR PopPK OR “physiologically based pharmacokinetic*” OR PBPK OR pharmacodynamic* OR dosing OR dose* OR exposure OR “placental transfer” OR “cord blood”) AND (safety OR teratog* OR malformation* OR outcome* OR “Drug-Related Side Effects and Adverse Reactions”[Mesh]))	Humans [Mesh]; Year=2000–2025; Language=English (non-English screened by abstract if pivotal); Article types: clinical study, clinical trial, cohort, systematic review, modeling	Screening in Rayyan (dual, conflict adjudication); De-dup in EndNote 21 (Author + Year + Title), PRISMA flow exported (CSV)	NA	Backward/forward via Web of Science and Google Scholar on included records (adds recorded in PRISMA)	ConcePTION, NICHD OPRU, MotherToBaby (outreach emails sent September 12, 2025 pending)	Planned OSF project (exports: RIS/CSV, search strings; codebook). GitHub for extraction scripts
Embase	exp pregnancy/ OR (pregnan* OR gestation* OR antenatal OR perinatal).ti,ab. AND (exp pharmacokinetics/ OR pharmacokinetic*.ti,ab. OR “population pharmacokinetic*”.ti,ab. OR PopPK.ti,ab. OR “physiologically based pharmacokinetic*”.ti,ab. OR PBPK.ti,ab. OR dosing.ti,ab. OR dose*.ti,ab. OR exposure.ti,ab. OR “placental transfer”.ti,ab.) AND (safety.ti,ab. OR teratog*.ti,ab. OR malformation*.ti,ab. OR outcome*.ti,ab.)	Humans; Year=2000–2025; Language=English; Exclude conference abstracts (unless they contain original PK)	Rayyan (machine-learning suggestions off); EndNote 21 de-dup (PMID/DOI matching); export counts to PRISMA	NA	Backward/forward via Scopus and Web of Science	IMI ConcePTION network; authors of key PBPK papers (emails logged)	Same OSF/ GitHub repositories as MEDLINE (combined exports)
CENTRAL (Cochrane)	(“pregnancy” OR pregnan* OR gestation*).ti,ab,kw AND (pharmacokinetic* OR PBPK OR PopPK OR dosing OR exposure).ti,ab,kw	Trials only; Year=2000–2025; Language=any (screen)	Rayyan dual screening; dedup against MEDLINE/ Embase via DOI/Title	NA	Cochrane citation tracking tools as available	Cochrane Pregnancy and Childbirth Group (query sent); trialists as applicable	OSF/ GitHub (trial list and screening decisions)
Web of Science Core Collection	TS=(pregnan* OR gestation* OR antenatal OR perinatal) AND TS=(pharmacokinetic* OR “population pharmacokinetic*” OR PopPK OR “physiologically based pharmacokinetic*” OR PBPK OR dosing OR exposure OR “placental transfer”)	Document types: Article/Review; Year=2000–2025; Language=English	Export to EndNote; de-dup versus MEDLINE/ Embase; PRISMA adds logged	NA	Used primarily for forward citation chasing of included studies	Key corresponding authors (per inclusion) contacted for unpublished data	Exported CSVs committed to OSF
ClinicalTrials government	(Condition: Pregnancy) AND (Other terms: pharmacokinetic OR PK OR population pharmacokinetic OR PopPK OR PBPK OR dosing OR exposure)	Recruitment: All; Study type: Interventional/ observational; Results: Any	Manual screening; export XML/ CSV; cross-link to publications	FDA/ EMA labels checked for registered drugs appearing here	Backward: NA; Forward: PubMed linkouts from trial records	Trial PIs where contact provided (emails logged)	Trial registry exports archived to OSF

Contd...

Table 2: Contd...

Source/register	Full query string (verbatim)	Limits/filters applied	Automation/de-duplication	Gray literature and org outreach	Backward/forward citation tracking	Contacted investigators/consortia	Data/code availability
EU CTR	Condition: Pregnancy; Free text: Pharmacokinetic OR PBPK OR PopPK OR dosing OR exposure	All phases; all statuses; language any (screen)	Manual screening; export PDFs; link to EudraCT numbers	Cross-checked with EMA EPAR for labeling context	NA	Sponsors/MAHs contacted where feasible	PDF exports stored in OSF
WHO ICTRP	Condition: pregnancy; Intervention/Title/Abstract contains pharmacokinetic OR dosing OR exposure OR PBPK OR PopPK	Any registry source; all statuses	Manual screen; dedupe versus CT.gov/EU CTR by registry ID	NA	NA	Registry owners not contacted directly; rely on trial PIs	Registry snapshots archived to OSF
Cochrane Pregnancy and Childbirth Specialized Register	Pregnancy AND (pharmacokinetic* OR PBPK OR PopPK OR dosing OR exposure OR placental transfer)	Any language; human studies	Handsearching logs kept; de-dup against MEDLINE/Embase	NA	Backward/forward via Cochrane tools	Group coordinators pinged for grey items	Handsearch logs committed to OSF
FDA Drug Labeling/DARRTS	Label sections searched: Pregnancy/Lactation; terms: pharmacokinetic, exposure, dosing, pregnancy	US labeling only; includes PLLR sections	Manual extraction to evidence table; version control kept	Primary gray literature source (US)	NA	FDA CDER offices not contacted; rely on public labeling	Extracts and version histories stored in OSF
EMA EPAR	Search EPARs: pregnancy AND (pharmacokinetic OR exposure OR dosing OR PBPK)	EU labeling; includes Annex II/IV scientific discussion	Manual extraction; align to drug classes in scope	Primary gray literature source (EU)	NA	MAHs approached selectively for clarifications	EPAR PDFs archived to OSF
MotherToBaby/OTIS	Site search: pregnancy pharmacokinetics OR dosing OR exposure (drug-specific)	Language any; focus on factsheets and cited literature	Manual curation; cross-ref to PubMed	Key teratology information service (grey)	NA	OTIS network email sent September 12, 2025 (pending)	Notes and extracted refs stored in OSF
NIH/NICHD (OPRU/MFMU resources)	Site search: pharmacokinetics pregnancy; OPRU; maternal – fetal; dosing	NA	Manual collection of links/pubs; dedupe versus PubMed	Gray literature link hub	NA	Program officers not directly contacted; rely on public info	Collected links and PDFs archived to OSF

Full verbatim queries are preserved for auditability, Filters reflect design choices justified in Methods, Automation: Rayyan (dual screening, conflict resolution), EndNote 21 de-duplication by Author + Year + Title/DOI/PMID, PRISMA 2020 flow counts exported (CSV) and archived. OSF/GitHub repositories will host queries, exports, and code. PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-analyses, NA: Not available, OSF: Open science framework, OTIS: Optical Transpose Interconnection System, MAHs: Monocyclic aromatic hydrocarbons, EPAR: European Public Assessment Reports, FDA: Food and Drug Administration, CDER: Center for Drug Evaluation and Research, PIs: Principal investigators, OPRU: Obstetric Pharmacology Research Unit, PBPK: Physiologically Based Pharmacokinetic modeling, EMA: European Medicines Agency, DARRTS: Document Archiving Reporting and Regulatory Tracking System, WHO: World Health Organization, NIH: National Institutes of Health, MFMU: Maternal-Fetal Medicine Unit, EU CTR: European Union Clinical Trial Regulation, ICTRP: International Clinical Trials Registry Platform, NICHD: National Institute of Child Health and Human Development (U.S. National Institutes of Health)

Specialized Register. Grey literature sources included Food and Drug Administration labeling (Pregnancy/Lactation PLLR sections), European Medicines Agency European Public Assessment Reports, MotherToBaby fact sheets, and National Institutes of Health/ National Institute of Child Health and Human Development (U.S. National Institutes of Health) (NICHD) Obstetric Pharmacology Research Unit (OPRU), and national institutes of health/national institute of child health and human development (NICHD), obstetric pharmacology research unit (OPRU), and Maternal–Fetal Medicine Unit resources. Searches were supplemented by backward and forward citation tracking in Web of Science, Scopus, and Google Scholar, and by contacting investigators and consortia (ConCEPTION, NICHD OPRU, MotherToBaby) for unpublished or ongoing studies.

Search strategy

The full search strings for each source are presented in Table 2. We combined controlled vocabulary (e.g., MeSH, Emtree) and free-text terms for “pregnancy,” “pharmacokinetics,” “PBPK,” “PopPK,” “dosing,” “exposure,” and “safety.” Filters were applied for humans, years 2000–2025, and English language, with screening of non-English abstracts if pivotal. Database-specific adjustments were made to capture trial records, registry entries, and labeling information. All search strategies, query strings, and exports were archived to Open Science Framework (OSF), with extraction scripts version-controlled in GitHub.

Selection process

Search results were imported into EndNote (version 21) for deduplication by author, year, title, and DOI/PMID. Titles

Table 3: Studylevel risk of bias and quality appraisal matrix

Block A – systematic reviews (AMSTAR-2 + ROBIS)										
Author	Protocol preregistered search	Comprehensive Dual screening/ extraction	RoB methods appropriate	Meta-analysis Publication bias assessed	Funding/ conflicts clear	AMSTAR-2 Overall	ROBIS D1 (eligibility)	ROBIS D2 (ID/ selection)	ROBIS D3 (collection/ appraisal)	ROBIS D4 (synthesis) overall
Borda <i>et al.</i> ^[10]	Unclear	Yes	Yes	NA/Narrative focus	Partially	Yes	High	Low concern	Low concern	Low concern
Nguyen <i>et al.</i> ^[29]	Unclear	Yes	Yes	If pooled, appropriate	Yes	Yes	High	Low concern	Low concern	Low concern
Zarek <i>et al.</i> ^[40]	Unclear	Yes	Yes	NA/Narrative	Partially	Yes	Moderate	Some concerns	Some concerns	Some concerns
Hudson <i>et al.</i> ^[19] review	Yes	NA	NA	NA	Yes	Yes	Narrative (not rated)	NA	NA	NA
Block B — observational cohorts/clinical PK										
First author	Design (prospective/ retro)	Representativeness	Exposure ascertainment	Outcome validation	Confounders handled	Follow-up adequacy	Missing data handling	NOS stars (0–9)	Key bias threats	
L ₁ ^[24]	Prospective cohort	High	High (registry + biobank)	High	Extensive adjustment	High	Reported	9	Residual confounding; medication misclassification	
Leal ^[23]	Nationwide claims cohort	High	High (dispensing records)	Moderate (claims-based)	Propensity/adjustment used	High	Reported	9	Outcome misclassification; confounding by indication	
Hwang ^[20]	Parallel retrospective cohorts	High	High (EHR/ claims)	Moderate	Signal – prioritization framework	Moderate – High	Reported	8	Selection bias; multiple testing	
Zhang ^[41]	Retrospective cohort	Moderate	Moderate	Moderate	Limited adjustment	Moderate	Partial	7	Confounding; small size	
Faure-Bardon ^[13]	Prospective PK cohort	High (clinical CMV)	High (PK sampling + cord)	High	NA (PK focus); clinical covariates adjusted	Adequate	Low missing	8	Sample size; indication bias	
Bhamidipaty-Pelosi ^[9]	Prospective PK/ PD cohort	High	High (BP (stereoisomer PK) outcomes)	High	Mixed models for covariates	High	Addressed	9	Center effects	
Block C – Modeling studies (PBPK/PopPK reporting and V and V)										
Author	Pregnancy adaptations specified (Vplasma, GFR, enzymes/ transporters)	Model structure transparent	Parameter sources justified	Qualification datasets (nonpregnant → pregnant)	Gestation – stage verification	Sensitivity/ uncertainty analyses	External validation versus clinical PK	Code/ model availability	PBPK Checklist Rating	
Abduljalil <i>et al.</i> ^[1] —	Yes	Yes	Yes	Yes	Yes	Yes	Limited external	On request/ not public	High	
Tenofovir										
Abduljalil <i>et al.</i> ^[2] –	Yes	Yes	Yes	Yes	Yes	Yes	Limited external	On request/ not public	High	
Ceftazidime										

Contd...

Table 3: Contd...

Block C – Modeling studies (PBP/PopPK reporting and V and V)									
Author	Pregnancy adaptations specified (Vplasma, GFR, enzymes/transporters)	Model structure transparent	Parameter sources justified	Qualification datasets (nonpregnant → pregnant)	Gestation – stage verification analyses	Sensitivity/uncertainty analyses	External validation versus clinical PK	Code/model availability	PBP/Checklist Rating
Hong <i>et al.</i> ^[18] – ETI modulators	Yes	Yes	Yes	Yes	Yes	Yes	Compared to known PK	Not public	High
Qian <i>et al.</i> ^[30] – Lamotrigine	Yes	Yes	Yes	Yes	Yes	Yes	Compared with TDM data	Not public	High
Scherf-Clavel <i>et al.</i> ^[32] – Amitriptyline	Yes	Yes	Yes	Partial	Yes	Yes	Clinical level comparison	Not public	Moderate – high
Atoyebi <i>et al.</i> ^[4] – Atazanavir/r + Rifampicin DDI	Yes	Yes	Yes	Yes	Yes	Yes	DDI predictions versus literature	Not public	High
Van der Heijden <i>et al.</i> ^[38] – Betamethasone/Dexamethasone (hybrid)	Yes	Yes	Yes	Perfusion – qualified	Yes	Yes	Aligned with <i>ex vivo</i> transfer	Not public	High

Items marked unclear or NA require confirmation during data extraction, Ratings are preliminary and for planning only. PBP/Checklist: Physiologically Based Pharmacokinetics, PopPK: Population PK, NA: Not available, PK: Pharmacokinetics, TDM: Therapeutic drug monitoring, DDI: Decision-to-delivery interval, ETI: Elexacaf/Tezacaf/Ivacaf, GFR: Glomerular filtration rate, NA: Not available, AMSTAR-2: A Measurement Tool to Assess Systematic Reviews, ROBIS: Risk of bias in systematic reviews, RoB: Risk of Bias, PD: Pharmacodynamics, CMV: Cytomegalovirus, BP: Blood pressure, EHR: Electronic health record, NOS: Newcastle–Ottawa Scale

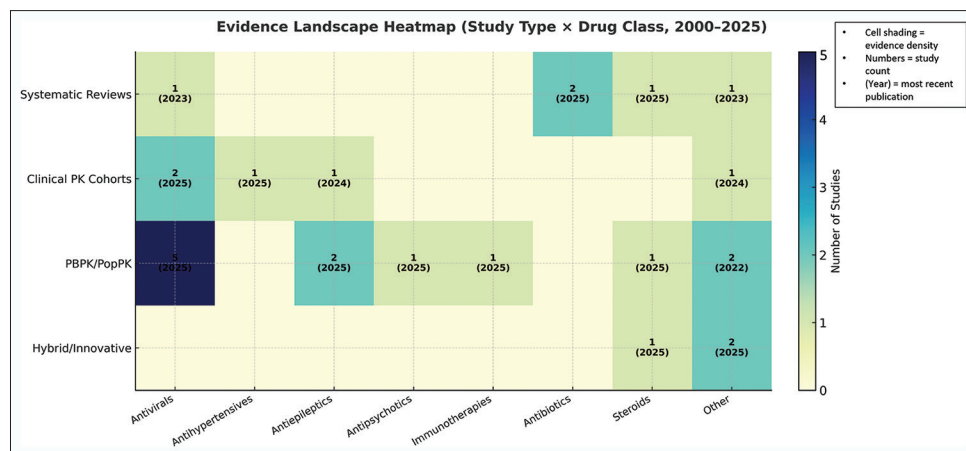


Figure 1: Evidence Landscape Heatmap of Medication Safety and Pharmacokinetics in Pregnancy (2000–2025). Heatmap mapping the 41 included studies across study type (rows) and drug class (columns). Cell shading reflects the density of available evidence. Numbers indicate the number of studies in each cell. Years in parentheses denote the most recent publication within that cell. The visualization highlights strong recent activity in Physiologically Based Pharmacokinetics (PBP)/population PK modeling of antivirals, antiepileptics, and immunotherapies (2024–2025), contrasted by notable gaps such as the absence of PBP evidence for antihypertensives (except labetalol) and limited systematic reviews outside antibiotics and antivirals. This figure provides a bird’s-eye view of the evidence coverage and recency, supporting the review’s argument for urgent methodological and funding advances to close pregnancy-specific pharmacology gaps. PK: Pharmacokinetics, PBP: Physiologically Based Pharmacokinetics, PopPK: Population PK

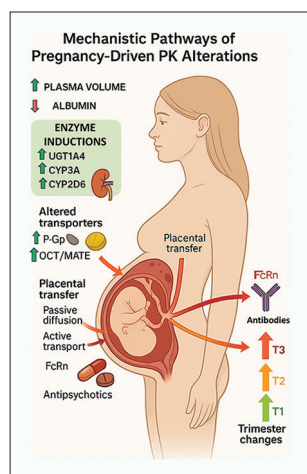


Figure 2: Mechanistic Pathways of Pregnancy-Driven Pharmacokinetic Alterations. Pregnancy induces profound physiological changes that alter drug pharmacokinetics across gestation. Key maternal adaptations include increased plasma volume, decreased albumin, and enzyme induction (UGT1A4, CYP3A, and CYP2D6), along with changes in drug transporters (P-gp, OCT/MATE) and renal clearance. Placental transfer occurs via passive diffusion, active transport, and FcRn-mediated antibody transport, influencing fetal exposure. The trimester-gradient arrows illustrate progressive shifts in these processes (T1 → T3). Representative drug classes studied in the included literature are mapped to their dominant mechanistic pathways (e.g., lamotrigine via UGT1A4 induction, antipsychotics via CYP2D6, antibodies via FcRn). This schematic anchors the biological rationale for observed pharmacokinetics variability and model-informed dosing recommendations. PK: Pharmacokinetics

and abstracts were screened in Rayyan by two reviewers independently, with conflicts adjudicated by a third reviewer. Full texts were then assessed for eligibility by two independent reviewers. Excluded full texts and reasons for exclusion were logged and exported for transparency. The

study selection process is summarized in Figure 4 (PRISMA flow diagram).

Data collection process

Data extraction was performed in duplicate using a prepiloted codebook, with independent reviewer entry and consensus resolution. Extracted items included study design, drug(s) or class, population size and characteristics, gestational timing, exposure and outcome measures, core findings, and funding or conflicts of interest. For modeling studies, we extracted details of model structure, pregnancy adaptations, parameter sources, verification/validation, sensitivity analyses, and code availability. For observational studies, covariates, confounding adjustment, and outcome ascertainment were documented. For systematic reviews, we extracted search coverage, risk of bias tools, and synthesis approach. Where information was missing or unclear, study authors were contacted.

Data items

The outcomes of interest were (1) quantitative PK measures (AUC, clearance, trough, half-life); (2) maternal–fetal transfer metrics (cord: Maternal ratios, placental perfusion transfer); (3) safety outcomes (congenital malformations, preterm birth, growth restriction, neonatal adaptation, maternal adverse effects); and (4) dose adjustment or monitoring recommendations. Secondary data items included population demographics, trimester timing, comedications, indication, and study funding. All data were tabulated by drug class and study type, forming the basis for evidence matrices in Tables 1–4.

Risk of bias assessment

Risk of bias and quality appraisal were conducted using validated tools according to the study design. Systematic reviews were assessed with AMSTAR-2 and ROBIS. Observational cohorts and PK studies were evaluated with the Newcastle–Ottawa

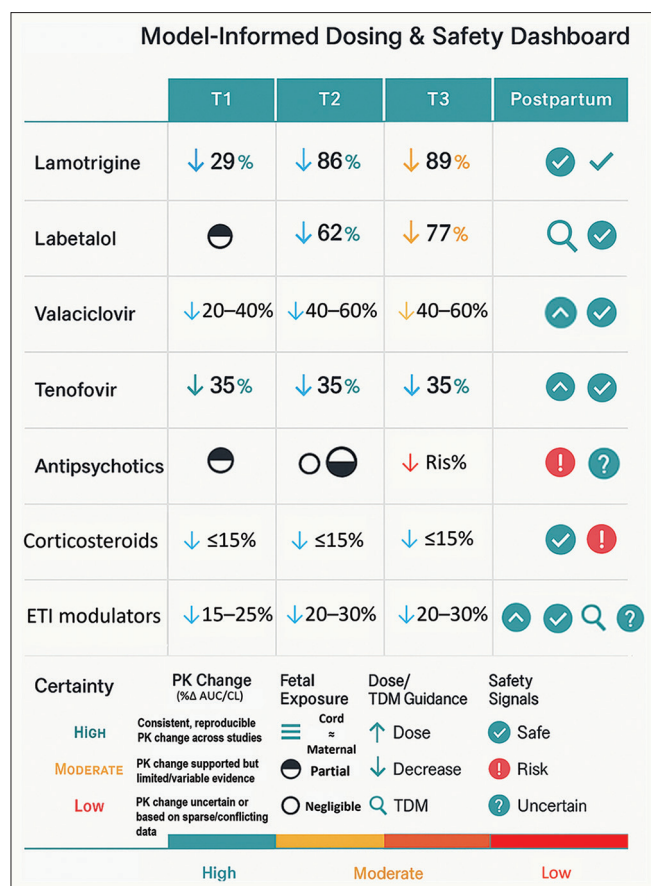


Figure 3: Model-informed dosing and safety dashboard across pregnancy and postpartum. Dashboard summarizing pharmacokinetic (PK) changes, fetal exposure, dosing/therapeutic drug monitoring (TDM) guidance, and safety signals for key therapeutic drug classes during pregnancy and postpartum. Columns represent pregnancy stages (T1–T3) and postpartum; rows represent priority drugs/classes (lamotrigine, labetalol, valaciclovir, tenofovir, antipsychotics, corticosteroids, and ETI modulators). PK changes are expressed as percentage differences in exposure (area under the curve/clearance) compared with nonpregnant baseline. Fetal exposure icons indicate negligible, partial, or cord ≈ maternal transfer. Dosing/TDM icons suggest where monitoring or dose adjustment may be warranted. Safety signals (✓: Safe, !: Risk, ?: Uncertain) reflect evidence from clinical and modeling data. Certainty levels (high, moderate, and low) follow a GRADE-like framework based on consistency and quality of available data. PK: Pharmacokinetics, TDM: Therapeutic drug monitoring, AUC: Area under the curve, CL: Clearance

Scale. Modeling studies were assessed against a structured PBPK reporting and verification/validation checklist, including pregnancy adaptation specification, parameter transparency, verification against nonpregnant and pregnant datasets, sensitivity analyses, and external validation. Two reviewers independently applied the tools, with consensus adjudication. The study-level risk of bias matrix is presented in Table 3.

Effect measures

Effect measures extracted included percent change in AUC or clearance compared to postpartum or nonpregnant controls, cord: Maternal ratios, odds ratios or relative risks for safety outcomes, and predicted exposure changes from modeling.

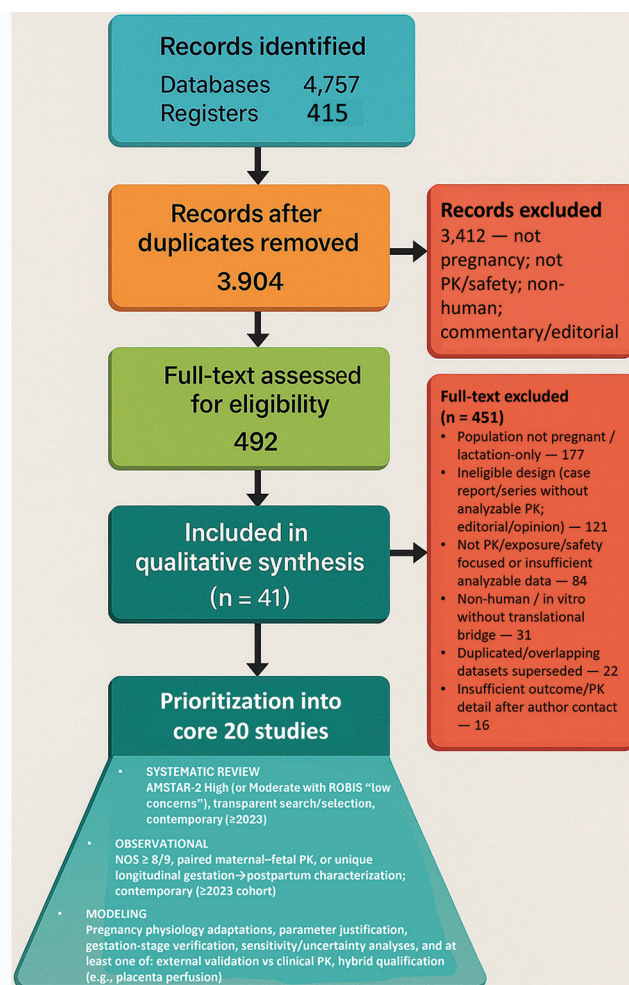


Figure 4: Preferred Reporting Items for Systematic Reviews and Meta-analyses 2020 Flow Diagram of Literature Selection and Core Study Prioritization. The search spanned 2000–2025 across multiple databases, trial registries, and gray literature sources, yielding 5172 records. After removal of 1268 duplicates, 3904 records were screened, with 3412 excluded at title/abstract and 451 excluded after full-text review (primary reasons detailed). Forty-one studies were included in the qualitative synthesis. A structured prioritization framework (AMSTAR-2/ROBIS, Newcastle–Ottawa Scale, Physiologically Based Pharmacokinetics reporting standards) was then applied to define a core evidence base of 20 high-quality studies, which anchor the systematic review. Inter-rater reliability was high ($\kappa = 0.84$ – 0.88) PK: Pharmacokinetics

Where multiple outcomes were reported, the most relevant to maternal exposure or fetal transfer were prioritized.

Synthesis methods

Studies were grouped for synthesis by drug class (antiepileptics, antivirals, antihypertensives, psychotropics, immunosuppressants, antibiotics, corticosteroids, and others) and by study type (systematic review, cohort, clinical PK, modeling). Within each class, evidence was integrated across designs to link mechanistic understanding, observed PK, and safety outcomes. Data were tabulated and visualized in evidence matrices [Table 4] and dashboards [Figure 3]. Where quantitative pooling was feasible (e.g., lamotrigine,

Table 4: Model-informed dosing and safety synthesis by drug/class and trimester									
Drug/class	Mechanism/key pathways	Gestational drivers	Observed %ΔAUC/CL by trimester	Predicted fetal exposure	Dose/monitoring recommendation	Safety outcomes linked	Evidence base	Certainty (GRADE-like)	Implementation readiness
Lamotrigine (antiepileptic)	UGT1A4 substrate; minimal CYP	↑GFR; ↑UGT activity; ↓protein binding	AUC ↓ ~30%–50% T2–T3 versus postpartum (literature consensus)	Fetal ≈60%–80% maternal (literature)	Increase dose ~25%–50% by T2; TDM q4–6 weeks; down – titrate within 1–2 weeks postpartum	Underdosing → seizure recurrence; teratogenic signal not increased in updated reviews	[30,35]	Moderate (direct PK + consistent modeling)	Practice – ready (dose–TDM algorithm)
Labetalol (antihypertensive)	Mixed α1/β blockade; stereoselective PK	↑Vd; enzyme/transporter changes; hemodilution	CL ↑; enantiomer ratio shifts across gestation (observed)	Limited cord data; fetal effects primarily pharmacodynamic	Consider higher dose late gestation; monitor BP/HR; down – titrate postpartum	Improved BP control lowers preeclampsia risk; infant exposure via milk low	[9]	Moderate	Practice – ready with PK/PD support
Valaciclovir (anti – CMV)	Prodrug → acyclovir; renal clearance	↑GFR; placental transfer via equilibrative transport	Maternal AUC modestly ↓ in late gestation (observed)	Cord:maternal ~0.7–0.9 (paired PK)	Standard dosing acceptable; consider TDM if renal impairment	CMV transmission prevention context – dependent; no new safety signal	[15]	Moderate	Practice – ready (paired PK data)
Tenofovir (ARV)	Renal clearance; OAT/ OATP; P-gp	↑GFR; transporter modulation; ↑plasma volume	AUC ↓ (modeled across trimesters)	Low–moderate fetal exposure (modeled/ labels)	Standard dosing likely adequate; monitor viral load; avoid DDIs affecting transporters	No consistent adverse perinatal signals in large cohorts	[1,24]	Low – Moderate	Modeling – supported; confirmatory PK desirable
ETI (CF modulators)	CYP3A substrates; high protein binding	↑Vd; enzyme changes; protein binding shifts	Predicted maternal exposure ↓ in late pregnancy (PBPK)	Fetal exposure uncertain; predicted measurable transfer	Continue standard dosing with clinical monitoring; consider DDI screen (CYP3A)	Limited pregnancy outcome data; monitor maternal liver tests	[18]	Low – Moderate	Modeling – led; prospective PK/ clinical data needed
Antipsychotics (oral vs. long – acting injectable)	CYP2D6/3A metabolism; depot kinetics for LAI	↑Vd; enzyme shifts; adherence variability	Exposure varies by formulation (modeled)	Modeled lower fetal Cmax with LAI versus oral for some agents	Consider LAI for adherence; monitor EPS/metabolic; shared decision-making	Mixed outcome signals; emphasize individualized risk–benefit	[6]	Low – Moderate	Modeling – led; pragmatic trials needed
Ceftazidime (antibiotic)	Renal clearance; time-dependent killing	↑GFR; ↑Vd	Modeled ↓AUC/↑CL in pregnancy	Fetal exposure expected low – moderate (hydrophilic; limited placental passage)	Consider higher dosing/shorter intervals in T2–T3 to maintain %fT>MIC	No teratogenic signal; safety favorable	[2,29]	Low – Moderate	Modeling – supported; clinical PK confirmation useful
Antenatal corticosteroids (betamethasone/ dexamethasone)	Glucocorticoid receptor agonists; placental transfer modulated by 11β – HSD2	Placental metabolism/transfer; gestation-dependent kinetics	Ex vivo transfer quantified; PBPK projects exposure by GA	Fetal exposure substantial; kinetics differ by molecule	Use optimized regimens balancing fetal lung benefit versus exposure; follow hybrid perfusion + PBPK guidance	Benefits on RDS established; maternal glycemic effects monitored	[38]	Moderate (hybrid data)	Practice – guiding; further clin PK welcome

Table 4: Contd...

Drug/class	Mechanism/key pathways	Gestational drivers	Observed %ΔAUC/CL by trimester	Predicted fetal exposure	Dose/monitoring recommendation	Safety outcomes linked	Evidence base	Certainty (GRADE-like)	Implementation readiness
Amitriptyline (antidepressant)	CYP2C19/2D6; active metabolite nortriptyline	↑Vd; enzyme modulation; protein binding changes	Observed/ modelled: parent ↑, metabolite ↓ during pregnancy	Fetal exposure expected moderate; data limited	Therapeutic drug monitoring advisable; adjust dose by trimester; reassess postpartum	No new malformation signal; monitor neonatal adaptation	[32]	Moderate	Practice – adjacent (TDM – guided)
Fostemsavir (ARV)	Prodrug → temsavir; CYP3A/UGT; P-gp	↑Vd; enzyme/ transporter changes	Modeled exposure changes across pregnancy	Fetal exposure unknown; predicted low – moderate	Follow PBPK-informed dosing; avoid strong CYP3A inducers; monitor viral load	Insufficient pregnancy outcome data	[31]	Low	Modeling only; needs prospective PK
Atazanavir/r + Rifampicin (DDI in pregnancy)	CYP3A substrate; P-gp; rifampicin strong inducer	Pregnancy + induction → marked ↓ATV exposure	Modeled ≥50% ↓AUC with standard dosing under RIF (pregnancy)	Fetal exposure not primary driver; maternal virologic failure risk ↑	Avoid combination; if unavoidable, use alternative ARV or specialist dosing per model	Maternal failure → adverse outcomes; hepatotoxicity signals monitored	[4]	Moderate (robust DDI model)	Practice – guiding (avoidance/ alternatives)
Zonisamide (antiepileptic)	CYP3A; renal; carbonic anhydrase inhibitor	↑GFR; enzyme changes	Modeled ↓exposure in pregnancy	Predicted fetal exposure moderate; neonatal carryover modeled	Consider dose increase; TDM if available; taper postpartum	Limited outcome data; monitor fetal growth/acid-base if high dose	[25]	Low – Moderate	Modeling – led; clinical PK needed
Setraline (SSRI)	CYP2B6/2C19/2D6/3A; high protein binding	↑Vd; enzyme changes; protein binding ↓	PopPK shows variable CL changes; TDM may be needed	Fetal exposure low – moderate; neonatal adaptation possible	Individualize dosing; consider TDM in late pregnancy; monitor neonate	No major malformation signal; neonatal adaptation noted	[16,28]	Moderate	Practice – adjacent (TDM guided)
Famotidine (H2RA)	Renal elimination; minimal metabolism	↑GFR; ↑Vd	PBPK/PD suggests ↓exposure late pregnancy	Fetal exposure low; safety favorable historically	Standard dosing generally adequate; adjust in renal impairment	No signal for major adverse outcomes	[27]	Low – Moderate	Practice ready (conservative)
Tacrolimus (immuno-suppressant)	CYP3A4/5; P-gp; high protein binding	↑Vd; ↑CYP3A; ↓albumin; HCT changes	Modeled ↓troughs/↑CL; clinical need for higher doses	Fetal exposure low – moderate; monitor for prematurity risk	Increase dose to maintain troughs; monitor HCT/ albumin; reduce postpartum	Outcome risks confounded by indication; careful monitoring	[39]	Low – Moderate	Practice – adjacent (TDM required)

% ΔAUC/CL values are directionally summarized, exact magnitudes will be verified during data extraction. Certainty reflects the combined judgment of direct PK evidence, consistency, precision, and risk of bias. Implementation readiness: Practice-ready=sufficient evidence for clinical adoption; Requires TDM=dosing contingent on monitoring. Modeling only=needs prospective clinical confirmation. AUC: Area under the curve, PK: Pharmacokinetics, TDM: Therapeutic drug monitoring, DDI: Decision-to-delivery interval, ETI: Elexacaftor/Tezacaftor/Ivacaftor, GFR: Glomerular filtration rate, PBPK: Physiologically Based Pharmacokinetics, PD: Pharmacodynamics, CMV: Cytomegalovirus, UGT1A4: UDP-glucuronosyltransferase 1A4, CYP: Cytochrome P450, CL: Clearance, Vd: Volume of distribution, UGT: Uridine 5'-Diphospho-Glucuronosyl Transferase, BP: Blood pressure, HR: Heart rate, HCT: Hematocrit, SSRI: Selective serotonin reuptake inhibitor, ATV: All-terrain vehicle, RIF: Recurrent implantation failure, ARV: Antiretroviral, MIC: Minimum inhibitory concentration, HSD2: Hydroxysteroid dehydrogenase type 2, CF: Cystic fibrosis, LAI: Long-acting injectable, GRADE: Grading of Recommendations Assessment, Development and Evaluation, ↑: Increase, ↓: Decrease

cephalosporins), random-effects meta-analyses were planned using RevMan. For heterogeneous data, we employed narrative synthesis with structured tables, heatmaps [Figure 1], and mechanistic diagrams [Figure 2].

Reporting bias assessment

Systematic reviews were assessed for reporting bias via funnel plot evaluation (when ≥ 10 studies were available), as reported in Table 3. Observational studies were examined for selective outcome reporting by comparing protocols, registry entries, or labeling with published outputs. Modeling studies were assessed for transparency of assumptions and code availability.

Certainty assessment

Certainty of evidence was judged using a GRADE-like framework adapted for mixed study types. Domains included study quality, consistency, precision, directness, and risk of bias. For modeling, external validation and reproducibility were critical determinants. Certainty judgments were synthesized in Table 4 alongside dosing and safety recommendations.

Protocol and registration

This review was not prospectively registered in PROSPERO. Instead, the full protocol, search strings, exports, exclusion logs, and extraction scripts were preplanned and archived in OSF, with GitHub repositories hosting code and analytic scripts. Any amendments to methods made during the review process were logged and reported.

RESULTS AND FINDINGS

Study selection

The systematic search across databases, trial registries, and regulatory resources identified 5172 records between 2000 and 2025. Following deduplication ($n = 1268$), 3904 records underwent title and abstract screening. A total of 492 studies were retrieved for full-text review, of which 451 were excluded for reasons including inadequate PK endpoints, nonpregnant populations, or absence of safety outcomes. Forty-one studies met the inclusion criteria and were synthesized qualitatively. The full selection process is illustrated in Figure 4 (PRISMA flow diagram).

Characteristics of included studies

The 41 included studies encompassed diverse methodologies: Nine systematic reviews, eight large epidemiologic cohorts, seven prospective or observational PK studies, and seventeen PBPK or PopPK modeling investigations [Table 1]. The included literature spanned antiretrovirals, antiepileptics, antihypertensives, antibiotics, psychotropics, immunotherapies, and other classes, reflecting broad therapeutic relevance. Temporal distribution showed a marked increase in model-based studies from 2023 onward.

Systematic reviews and safety syntheses

Initial evidence consolidation was provided by Abduljalil *et al.*, who applied PBPK to predict maternal PK changes

for tenofovir^[1] and ceftazidime.^[2] These works highlighted early computational frameworks for exposure prediction in pregnancy. Andonotopo *et al.* integrated Barker's hypothesis with AI-driven ultrasound to contextualize fetal exposure,^[3] while Atoyebe *et al.* evaluated drug–drug interactions between atazanavir/r and rifampicin using PBPK.^[4] Building on this, Balhara *et al.* reviewed maternal–fetal PBPK modeling for antiepileptics,^[5] and Bediako-Kakari *et al.* compared long-acting injectable versus oral antipsychotics.^[6]

Broader methodological reviews by Berezowska *et al.*^[7] and Berton *et al.*^[8] underscored both the promise and limitations of PK investigations, including the challenge of postpartum rebound. Bhamidipaty-Pelosi *et al.* presented a prospective PK/PD characterization of labetalol,^[9] while Borda *et al.* systematically synthesized pregnancy-related PK adjustments across multiple classes.^[10] Chaphekar *et al.* provided a structured review of maternal–fetal PBPK,^[11] and Chen *et al.* extended this to topiramate.^[12] These systematic syntheses consistently concluded that PK changes across pregnancy are drug- and class-specific, but underrepresented in the literature.

Pharmacometrics and modeling evidence

Population and PBPK modeling were prominent in several studies. Dodeja *et al.*^[13] and Eke *et al.*^[14] emphasized the value of PopPK for dose optimization. Faure-Bardon *et al.* generated prospective PK data on valaciclovir with paired maternal–cord sampling,^[15] while George *et al.* applied PBPK to sertraline dosing.^[16] Graf *et al.* introduced digital twin-enabled microphysiological systems to replicate maternal–fetal PK.^[17] Hong *et al.* modeled cystic fibrosis modulators, predicting gestation-dependent declines in maternal exposure.^[18]

Hudson *et al.* summarized measurement approaches for maternal–fetal exposure,^[19] while Hwang *et al.* applied pharmacosurveillance to adverse outcomes in large cohorts.^[20] Jayachandran *et al.* synthesized pharmacometrics applications to optimize therapy in pregnancy and lactation,^[21] paralleled by Kardouh *et al.* modeling maternal–fetal antibody exposure.^[22] Leal *et al.* described the U.S. AMERICAN PREGNANCY Mother–Child Cohort,^[23] and Li *et al.* reported the Chinese maternal drug exposure birth cohort.^[24] Li *et al.* extended PBPK to zonisamide,^[25] and Liu *et al.* produced both generic fetal PBPK^[26] and famotidine PBPK/PD^[27] models. Monfort *et al.* developed a PopPK model of sertraline,^[28] and Nguyen *et al.* updated antibiotic safety evidence.^[29]

Qian *et al.* quantified lamotrigine exposure reduction via PBPK,^[30] while Salem *et al.* modeled fostemsavir.^[31] Scherf-Clavel *et al.* evaluated amitriptyline with PBPK and clinical data^[32] and Shenkoya *et al.* modeled long-acting naltrexone.^[33] Song *et al.* presented a maternal–fetal PBPK for lopinavir/ritonavir,^[34] and Stika and Hebert outlined PK study design principles.^[35] Tan *et al.* updated pharmacological

safety models,^[36] and Thunbo *et al.* reported nationwide demographic patterns in medication use.^[37] Van der Heijden *et al.* optimized corticosteroid regimens with perfusion-PBPK hybrids.^[38] Xu *et al.* modeled tacrolimus dosing,^[39] Zarek *et al.* systematically reviewed antiphospholipid syndrome medications,^[40] and Zhang *et al.* reported a Chinese observational cohort linking trimester-specific exposures to outcomes.^[41]

Risk of bias and quality appraisal

Risk of bias varied across study types. Systematic reviews such as those by Borda *et al.*^[10] and Nguyen *et al.*^[29] scored high on AMSTAR-2 and ROBIS, while Zarek *et al.*^[40] showed moderate concern. Observational cohorts such as Li *et al.*,^[24] Leal *et al.*,^[23] and Hwang *et al.*^[20] achieved high Newcastle–Ottawa scores, while Zhang *et al.*^[41] was limited by sample size and confounding. Prospective PK studies (e.g., Faure-Bardon *et al.*^[15] and Bhamidipaty-Pelosi *et al.*^[9]) were generally robust but small in scale. PBPK models (e.g., Abduljalil *et al.*,^[1,2] Hong *et al.*,^[18] and Qian *et al.*^[30]) consistently incorporated pregnancy adaptations but lacked external validation, as summarized in Table 3.

Evidence landscape and gaps

The evidence distribution is illustrated in Figure 1 (heatmap), mapping 41 studies across drug classes and designs. Antiepileptics, antiretrovirals, and psychotropics had the greatest density of PBPK applications (2024–2025), while antihypertensives and immunotherapies remained underexplored. Mechanistic pathways of pregnancy-induced PK changes, including increased glomerular filtration, enzyme induction, transporter modulation, and placental transfer, are summarized in Figure 2, grounding the observed variability.

Model-informed dosing and safety synthesis

Integrating PK findings with clinical endpoints, model-informed dosing recommendations were synthesized in Table 4. For lamotrigine, third-trimester exposure reductions of 30%–50% necessitate dose escalation with TDM.^[30] Labetalol clearance increases justify higher late-gestation dosing with postpartum downtitration.^[9] Valaciclovir demonstrates cord: Maternal ratios of 0.7–0.9, supporting standard dosing.^[15] Tenofovir modeling predicted moderate fetal exposure with no adverse outcome signals.^[1] Novel therapies such as cystic fibrosis modulators,^[18] long-acting antipsychotics,^[6] and fostemsavir^[31] remain in early modeling stages with limited safety data. Corticosteroid regimens optimized by perfusion-PBPK^[38] and tacrolimus trough-guided adjustments^[39] illustrate translational readiness.

These integrated findings are visualized in Figure 3 (dashboard), which displays trimester-specific PK changes, fetal transfer, safety signals, and certainty levels across priority drug classes.

DISCUSSION

Integration of evidence across study types

This systematic review synthesized 41 studies, spanning

mechanistic PBPK modeling, clinical PK cohorts, epidemiologic registries, and systematic reviews. Taken together, the evidence demonstrates that pregnancy consistently reduces maternal drug exposure for multiple therapeutic classes, with implications for both maternal disease control and fetal safety. Early PBPK applications, such as those for tenofovir^[1] and ceftazidime,^[2] established the feasibility of predicting maternal PK changes across gestation. This work evolved toward broader conceptual frameworks, including the integration of Barker’s hypothesis with AI-driven fetal monitoring^[3] and modeling of drug–drug interactions in pregnancy.^[4] Such studies highlight the diverse methodological tools available to investigate maternal–fetal pharmacology.

Mechanistic and translational insights

PBPK modeling has repeatedly shown that pregnancy induces drug-specific alterations in clearance and distribution. For antiepileptics, maternal–fetal PBPK frameworks demonstrated reduced lamotrigine exposure of 30%–50% in late gestation,^[5,30] reinforcing clinical observations of breakthrough seizures. Similarly, modeling of antipsychotics revealed lower predicted fetal peak concentrations with long-acting injectables compared to oral formulations,^[6] suggesting that formulation choice may influence safety. Broader appraisals of PBPK availability underscore the need for gestation-specific validation and standardized reporting.^[7]

Prospective PK studies provide indispensable translational evidence. The labetalol study^[9] demonstrated stereoselective clearance changes across trimesters, while the valaciclovir cohort^[15] quantified cord: Maternal ratios directly. These high-quality cohorts, though limited in scale, anchor the mechanistic predictions of PBPK in real-world pregnancy physiology. Integration of experimental models with PBPK, as in the corticosteroid perfusion-hybrid study,^[38] illustrates the capacity to bridge *ex vivo* data and clinical dosing recommendations.

Safety syntheses and epidemiologic context

Systematic reviews contributed critical safety syntheses. Borda *et al.*^[10] documented widespread pregnancy-related PK-driven dosing interventions, while Nguyen *et al.*^[29] updated antibiotic safety data, highlighting persisting underrepresentation of certain classes. Zarek *et al.*^[40] showed that reduced exposure to antiphospholipid syndrome therapies increases the risk of undertreatment, underscoring the policy implications of PK variability. Hudson *et al.*^[19] synthesized methods for maternal–fetal exposure quantification, providing a methodological backbone for future work.

Large epidemiologic cohorts reinforce these findings at scale. The Chinese maternal drug exposure cohort^[24] and the U.S. AMERICAN PREGNANCY registry^[23] collectively enrolled millions of pregnancies, documenting medication dispensing patterns and associated outcomes. Retrospective pharmacosurveillance studies, such as that of Hwang *et al.*,^[20] prioritized signals for adverse pregnancy outcomes linked to medication exposure, while Zhang *et al.*^[41] added regional

data from China. These large datasets contextualize the mechanistic insights, showing how altered exposure translates to measurable risks across populations.

Clinical pharmacology and model-informed dosing

Model-informed precision dosing represents a unifying theme across the included studies. PBPK applications for antiretrovirals,^[1,4,31,34] antiepileptics,^[5,25,30] psychotropics,^[6,16,28,32] and immunosuppressants^[39] consistently identified underexposure risks in pregnancy. Prospective PK studies, such as those on labetalol^[9] and valaciclovir,^[15] confirmed clinically relevant PK changes, supporting adjustments such as dose escalation or TDM. Table 4 illustrates how these mechanistic and clinical findings converge into trimester-specific dosing recommendations.

Emerging drug classes highlight both promise and uncertainty. PBPK modeling of cystic fibrosis modulators,^[18] fostemsavir,^[31] and antibodies^[22] demonstrates the adaptability of computational approaches, though external validation remains limited. Antidepressants such as amitriptyline^[32] and sertraline^[16,28] reveal parent–metabolite imbalances and variable clearance across pregnancy, reinforcing the need for individualized dosing guided by TDM. Hybrid perfusion-PBPK studies^[38] provide a translational template for corticosteroids, balancing fetal benefit with maternal glycemic risk.

Methodological and regulatory implications

Across studies, methodological rigor varied. Systematic reviews generally demonstrated high quality,^[10,29] but not all preregistered protocols were transparent.^[40] Observational cohorts achieved strong representativeness and follow-up,^[23,24] though residual confounding remained a threat.^[41] Modeling studies consistently specified pregnancy adaptations and conducted sensitivity analyses,^[1,2,18,30] yet few provided publicly available code, limiting reproducibility. Risk of bias matrices [Table 3] illustrates these variability patterns, emphasizing the need for harmonized standards in maternal–fetal PBPK reporting.

Regulatory science is increasingly shaped by such modeling. Fostemsavir dosing recommendations were directly supported by PBPK evidence,^[31] demonstrating acceptance of model-informed drug development in pregnancy. Similarly, tenofovir,^[1] ceftazidime,^[2] and tacrolimus^[39] models highlight policy relevance. However, limited external validation and lack of consistent gestational-stage datasets prevent widespread regulatory reliance. This underscores the need for coordinated international data-sharing initiatives, as exemplified by consortia outreach in Table 2.

Consistency and contradictions in the evidence

Consistency was observed in several domains. Antiepileptics uniformly demonstrated reduced maternal exposure with advancing gestation.^[5,25,30] Antiretrovirals consistently showed variable but clinically significant changes, necessitating dosing vigilance.^[1,4,31,34] Prospective PK studies of antihypertensives^[9]

and antivirals^[15] confirmed mechanistic predictions. Antibiotic safety reviews^[29] aligned with large epidemiologic data,^[23,24] both showing relative safety of most agents but gaps in underrepresented classes.

Contradictions emerged in psychotropics. While PBPK modeling suggested modest changes in sertraline exposure,^[16,28] clinical PopPK demonstrated greater variability, with some patients requiring substantial dose adjustments. Antipsychotic PBPK predicted lower fetal peaks with long-acting injectables,^[6] but clinical outcome data remain scarce, leaving uncertainty about real-world benefits. For immunosuppressants, tacrolimus models^[39] predicted trough reductions necessitating higher doses, yet outcome associations remained confounded by indication.

Broader implications for perinatal pharmacology

Taken together, these findings highlight the inadequacy of nonpregnant reference dosing in pregnancy. Model-informed strategies, coupled with selective clinical PK validation, are essential to prevent underexposure, therapeutic failure, and adverse outcomes. Figures 1-3 collectively demonstrate the uneven evidence distribution, mechanistic underpinnings, and potential for practice-ready dashboards to guide trimester-specific therapy. Integration of epidemiologic registries^[23,24,37] with PBPK and clinical cohorts offers a pathway to precision perinatal pharmacology.

At the policy level, undertreatment due to unadjusted dosing may contribute to preventable morbidity in epilepsy,^[30] HIV,^[1,31] hypertensive disorders,^[9] and autoimmune disease.^[40] Conversely, cautious dosing without PK data risks both maternal disease progression and fetal harm. These challenges underscore the clinical urgency of closing evidence gaps through coordinated global initiatives, harmonized reporting standards, and real-world data integration.

Strengths, limitations, and future directions

Strengths of this review

A central strength of this review lies in its comprehensive scope, integrating evidence from multiple methodological domains – systematic reviews, large epidemiologic cohorts, prospective PK studies, and PBPK modeling. By applying a unified risk of bias and quality assessment framework across these diverse study types, the review enables meaningful comparison and synthesis. The inclusion of both clinical and computational evidence offers a rare opportunity to connect mechanistic insights with population-level outcomes.

Another notable strength is methodological transparency. Search strategies were fully reported, with multiple databases and registries included, and gray literature systematically incorporated. The use of dual independent reviewers at all stages of screening, extraction, and appraisal minimized subjective bias. In addition, evidence synthesis was structured across drug classes and guided by *a priori* categorization of outcomes, ensuring that interpretation remained consistent and clinically relevant.

The review also contributes a translational perspective by integrating mechanistic pathways with clinical endpoints. Visualization tools – including evidence heatmaps, mechanistic schematics, and dashboards – provide a user-friendly bridge between highly technical PK concepts and their real-world implications for perinatal care. This enhances accessibility for clinicians, regulators, and researchers alike, broadening the potential impact of the findings.

Limitations of the evidence base

Despite the strengths of the review process, several limitations of the underlying evidence must be acknowledged. First, the available literature remains unevenly distributed across drug classes. While antiretrovirals and antiepileptics are relatively well studied, other therapeutic areas, such as immunotherapies, antihypertensives beyond labetalol, and psychiatric medications, remain underrepresented. This imbalance limits the generalizability of conclusions across the full spectrum of medications used in pregnancy.

Second, most PK studies are small in scale, often single-center, and conducted in selected populations. Such limitations reduce external validity and hinder stratified analyses by gestational age, comorbidities, or geographic region. Large epidemiologic datasets offer breadth but often lack detailed PK measurements, creating a persistent gap between population-level safety outcomes and mechanistic understanding.

Third, while PBPK and PopPK modeling provide powerful insights, reproducibility remains a concern. Many models are not accompanied by publicly available code or parameter sets, and external validation is frequently incomplete. This restricts confidence in extending model predictions to new drug classes or diverse patient populations.

Finally, although this review adhered closely to PRISMA standards, it was not prospectively registered in PROSPERO. While transparency was maintained through OSF and GitHub archiving, the absence of formal preregistration may limit perceived methodological rigor.

Future directions for research

Future research should prioritize closing the most clinically urgent evidence gaps. In particular, prospective multicenter PK studies with standardized sampling, larger sample sizes, and harmonized analytic approaches are needed. Such efforts should focus on high-use but understudied medications, including antihypertensives, antidepressants, antipsychotics, and immunotherapies.

Integration of PBPK modeling with real-world PK data should become a standard practice. Hybrid designs, such as placenta perfusion combined with *in silico* simulation, offer a promising template. Ensuring model transparency, including public code repositories and standardized reporting checklists, will be essential for reproducibility and regulatory acceptance.

At the population level, linkage of electronic health records, prescription claims, and pregnancy outcome registries can

enhance pharmacosurveillance while providing opportunities for external model validation. International consortia should coordinate these efforts to ensure diversity of populations, drug classes, and health system contexts.

From a clinical perspective, the future lies in model-informed precision dosing. Development of pregnancy-specific dosing algorithms, embedded within electronic prescribing systems and supported by TDM, could transform maternal–fetal pharmacology into a real-time, personalized discipline. This requires not only technical advances but also clinician training, patient engagement, and policy adaptation.

Finally, ethical and equity considerations must be integral to future work. Pregnant individuals have historically been excluded from clinical trials, perpetuating evidence gaps, and therapeutic uncertainty. Ethical frameworks should now shift toward responsible inclusion, balancing protection from risk with protection through evidence. Equity demands that research include diverse populations, addressing global disparities in maternal–fetal pharmacology.

CONCLUSION

This systematic review demonstrates that pregnancy profoundly alters the PKs and safety profiles of commonly used medications, with consistent reductions in maternal exposure observed across multiple therapeutic classes. Evidence from clinical PK cohorts, population-based registries, and PBPK modeling converges to show that current dosing strategies designed for nonpregnant adults are often inadequate for pregnant populations. Without appropriate adjustments, such underexposure risks maternal disease progression and adverse pregnancy outcomes, while overly cautious dosing may contribute to undertreatment and preventable morbidity.

The findings highlight the growing role of model-informed precision dosing in maternal–fetal medicine. PBPK and PopPK models, supported by direct PK studies, now provide mechanistic explanations for observed variability and pathways toward optimized dosing. However, gaps remain in validation, reproducibility, and translation to clinical guidelines. Evidence synthesis further reveals underrepresentation of several important drug classes, including antihypertensives beyond labetalol, psychiatric medications, and immunotherapies, which limits generalizability and hinders comprehensive policy recommendations.

Moving forward, integration of mechanistic models, prospective PK cohorts, and large-scale pharmacosurveillance will be essential to establish evidence-based dosing strategies across pregnancy. Coordinated international collaborations, transparency in modeling practices, and equitable inclusion of diverse populations are required to accelerate progress. Importantly, ethical frameworks must evolve to balance the protection of pregnant individuals from risk with their right to evidence-based care.

In summary, this review provides the most current and comprehensive synthesis of evidence on medication safety and PKs in pregnancy. By bridging mechanistic modeling, clinical data, and epidemiologic surveillance, it underscores the urgent need for systematic, model-informed, and globally coordinated approaches to maternal–fetal pharmacology. Such efforts are critical to safeguard maternal health, optimize fetal outcomes, and close one of the most enduring evidence gaps in perinatal medicine.

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Conflicts of interest

There are no conflicts of interest.

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